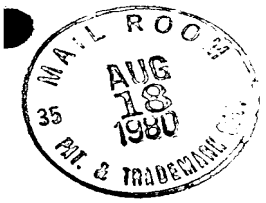


IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#10

Applicants : Peder Bernhard Berntsson et al.

Serial No. : 050,083 Examiner : Alan L. Rotman

Filed : June 19, 1979 Group Unit: 121

For : NEW 2, 6-DIMETHYL-4-2, 3-DISUBSTITUTED PHENYL-1, 4-DIHYDROPYRIDINE-3, 5-DICARBOXYLIC ACID-3, 5-ASYMMETRIC DIESTERS HAVING HYPOTENSIVE PROPERTIES, AS WELL AS METHOD FOR TREATING HYPERTENSIVE CONDITIONS AND PHARMACEUTICAL PREPARATIONS CONTAINING SAME

DECLARATION UNDER RULE 132

I, PEDER BERNHARD BERNTSSON, declare and say that:

I am a citizen of Sweden and reside at Flugsnapparegatan 17 A, S-43133 Mölndal, Sweden:

I was graduated from the University of Gothenberg in Göteborg, Sweden in 1964 with a B.Sc. in Chemistry; in 1968 I earned a Ph.L. in Organic Chemistry from the University of Gothenberg and in 1970, I earned a Ph.D. in Organic Chemistry from the same university after having defended my thesis;

I have been employed from 1968 to the present time by Aktiebolaget Hässle, a company located in Mölndal, Sweden where in 1968-1969 I was a group leader in the Department of Organic Chemistry and from 1970 to the present time I have been the head of this department.

I am the inventor or co-inventor of fifteen patents in the field of β-receptor blockers, antihypertensive agents, organic chemistry, gastric acid secretion inhibitors, and anti-depressive agents;

I am the co-author of eleven different papers, viz:

1) Berntsson, P., Wanger, M. and Carter, R.E. Acta Chem. Scand. 21 (1967) 879-888. Salts Effects on the Racemization of Biphenyls.

2) Berntsson, P. and Carter, R.E. Acta Chem. Scand. 22 (1968) 2141-2149. Salts Effects on the Racemization of Biphenyls.

3) Carter, R.E. and Berntsson, P. Acta Chem. Scand. 23 (1969) 499-503. Salts Effects on the Racemization of Biphenyls.

4) Carter, R.E. and Berntsson, P. Acta Chem. Scand. 22 (1968) 1047-1050. Comments on Some Contradictory Results of Polarimetric and NMR Studies of the Configurational Inversion of Several Biphenyl Derivatives.

5) Brändström, A., Berntsson, P., Carlsson, S., Djurhuus, A., Gustavii, K., Junggren, U., Lamm, B. and Samuelsson, B. Acta Chem. Scand. 23 (1969) 2202. Ion Pair Extraction in Preparative Organic Chemistry.

6) Berntsson, P., Brändström, A., Junggren, U., Palmer, L., Sjöstrand, S.E. and Wilander, B. Acta Pharm. Suec. 13 (1976) 385-390. Gastric acid secretion inhibitors.

7) Berntsson, P., Brändström, A., Junggren, U., Palmer, L., Sjöstrand, S.E. and Sundell, G. Acta Pharm. Suec. 14 (1977) 229-236. Gastric acid secretion inhibitors.

8) Longoni, R., Berntsson, P., Bild, N. und Hesse, M. Helv. Chim. Acta 60 Fasc. 1, (1977) 103-111. Der massenspektrometrische Verlust von Vinylalkohol aus 1-Amino-3-aryloxy-2-propanolen.

9) Anderson, G. and Berntsson, P. Acta Chem. Scand. B29 (1975) 948-952. Periodate Oxidation of Phenols. XVIII. Oxidation of 2-Methoxyphenols with Periodic Acid in Methanol.

10) Carter, R.S., Dahlqvist, K-I. and Berntsson, P. Org. Magn. Res. 9 (1977) No. 1, 44-48. N.m.r. Studies of a Rate Process in a Bridged Biphenyl: Resolution of a Discrepancy between N.m.r. and Polarimetric Kinetic Data.

11) Berntsson, P. and Samuelsson, G.B. Kemisk Tidskrift 1976:10, 48-50. β-blockerare - nya läkemedel mot hjärt- och kärlsjukdomar.

I am familiar with the above-identified patent application Serial No. 050,083 and with the Official Action of October 10,1979 in which claims 1-11 were rejected for being obvious over the references cited, viz United States Patents 3,441,648; 3,488,359; and 3,799,936.

In order to show the effects of the compounds of the present application and those of the compounds encompassed by the United States Patents 3,441,648; 3,488,359; and 3,799,936 the following tests were carried out using said compounds.

The tests were carried out in accordance with the description given in the present application on pages 19 and 20, viz:

The anti-hypertensive effect of the compounds was tested in conscious, unrested spontaneously hypertensive rats (SHR) of the Okamoto strain. The animals had been prepared by prior implantation of indwelling catheters in the abdominal aorta

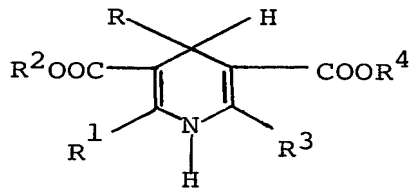
via the femoral artery. Mean arterial blood pressure (MABP) and heart rate were continuously monitored. After a two hour control period, the compounds under study were administered by oral intubation at two hour intervals, suspended in methocel solution (5ml/kg body weight). The cumulated doses were 1, 5 and 25 μmoles/kg body weight. The anti-hypertensive response, i.e., the blood pressure (BP) reduction to each dose, was expressed as a percentage of the initial control BP per BP level and plotted against the dose on a logarithmic scale. The dose which would give a 20 percent BP reduction was then determined by interpolation. The results are shown in Table I below.

The specificity towards smooth muscle relaxation was examined as follows: the isolated portal vein preparation of Wistar rats was mounted in an organ bath together with a paced isolated papillary heart muscle preparation of the same aminal. The integrated contractile activity of the portal vein smooth muscle and the peak force amplitude of the papillary myocardial preparation were recorded. The respective activities during a 30 minute control period were set as 100 percent and the ensuing activities under the influence of the agents under study were expressed as a percentage thereof. The agents were administered at 10 minute intervals and the potency for vasodilation (ED_{50} of portal vein) and that of myocardial depression (ED_{50} of papillary muscle) were determined by interpolation from the concentration-effect relationship determined in each experiment. A "selectivity" value was determined for each compound by ascertaining the ratio of the ED_{50} values for vasodilation and myocardial depression, respectively,

obtained in the experiments. This logarithmic selectivity value was transformed into numerical format and entered in Table I below.

In Table I below the Example numbers refer to Examples of the present application and capital letters denote a compound disclosed by one of the three cited references. These latter compounds were selected as being the closest structurally to the compounds of the present invention.

United States Patent No. 3,799,936 ('936) relates to asymmetric esters of substituted phenyl-1,4-dihydropyridines of the following formula:



wherein R is phenyl, optionally substituted with up to three substituents from the group alkyl, alkoxy, halogen, trifluoromethyl, and carboalkoxy, R^1 and R^3 are the same or different and are each hydrogen or alkyl, R^2 is alkyl, alkenyl, alkynyl, or alkoxyalkyl, R^4 is different from R^2 and is alkenyl, alkynyl or alkoxyalkyl.

The structure of 20 mono or trisubstituted phenyl compounds illustrated in the '936 patent have been examined and the compound represented by '936, Example 14 (wherein R=2-ClPh, R^1=CH_3, R^2=C_2H_5, R^3=CH_3 and R^4=β-methoxyethyl) has been tested. This compound is represented as compound A in Table I and it is most similar to the dichlorophenyl compounds of Examples 2, 8 and 13 in the specification in the present case wherein:

Example	R_1	R_2	R_3	R_4
2	$CH_2CH_2OCH_3$	C_2H_5	Cl	Cl
8	$CH_2CH_2OCH_3$	$CH(CH_3)_2$	Cl	Cl
13	CH_3	$CH_2CH_2OC_2H_5$	Cl	Cl

In addition to the foregoing prior art compound A, and with respect to the Examiner's objection given in the Office Action of April 24, 1980, on page 3 thereof, two additional compounds of the '936 patent have been tested, viz: 2,6-dimethyl-4-(2'-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-ethyl ester 5-β-propoxyethyl ester, (B), and 2,6-dimethyl-4-(2'-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-isopropylester 5-propargylester, (C).

The compounds represented by B and C in Table I below are most similar to the dichlorophenyl compound of Example 3 in the specification in the present case wherein

Example	R_1	R_2	R_3	R_4
3	CH_3	$CH(CH_3)_2$	Cl	Cl

as well as the compound of Example 8, shown above.

The compound represented by Example 2 has a selectivity ratio of 78, the compound of Example 3 shows a selectivity ratio of 56, the compound shown in Example 8 has a selectivity ratio of 107 and the compound according to Example 13 has a selectivity ratio of 66, whereby these compounds have a potency given as ED_{20} of 1 to 15 µmoles/kg, which combination of selectivity and potency makes these compounds clinically potential antihypertensive drugs. Since the compound A demonstrates a selectivity ratio of only 17 in combination with a high ED_{20}-value it is evident that the compound A is not a potential antihypertensive drug. Compounds B and C show a moderate selectivity ratio, whereby, however, these compounds show high ED_{20}-values, which are considerably higher than the ED_{20}-values of the present compounds. Thereby, these latter compounds are not potential antihypertensive drugs. It is thereby evident that the compounds of this invention are significantly, and unexpectedly more selective and potent than the compounds of the '936 patent.

TABLE I

(Comparison between compounds of the present invention, and compounds of U.S. Patent No. 3,799,936)

Compound according to Example	SHR ED_{20} µmoles/kg bodyweight	Ratio $\frac{\text{heart}}{\text{vasc.}}$
2	15	78
3	1	56
8	4	107
13	11	66
A	25	17
B	>125	61
C	24	79

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The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issuing thereon.

Further, declarant saith not.

Peder Bernhard Berntsson

Peder Bernhard Berntsson

Dated: 80-07-30

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